HF had an anxiety disorder [14]. Another report showed that the score for anxiety symptoms was higher in patients with HF than in healthy controls [15]. However, this issue has remained controversial [1]. In some studies, no association has been found between anxiety symptoms and cardiac events in patients with HF [16–19].

Recently, van den Broek et al. [20] focused on the impact of clustering psychosocial risk factors on clinical outcomes in patients with implantable cardioverter defibrillators (ICDs) and showed that ICD patients with both anxiety and Type D personality were at an increased risk of ventricular arrhythmia. In that study, the risk factors were clustered because psychological risk factors often occurred together, but not individually, and the clustering of psychological risk factors may pose a high-risk factor for clinical events than would a single risk factor in cardiac patients [20,21]. Although depression and anxiety have been discussed separately as psychological factors, they frequently cluster within a patient [22]. The signs and symptoms of anxiety are often present in patients with depression, and the two conditions may play a partial role in a pathophysiological process of HF [23]. Some studies have shown that the clustered depression and anxiety worsened patients' health status following myocardial infarction or percutaneous coronary intervention [24,25]. From this viewpoint, clustered depression and anxiety may be clinically valuable as an indicator of psychological distress in patients with HF. However, a few studies have investigated this issue. The aim of this study was to evaluate the effect of clustered depression and anxiety on mortality and rehospitalization in patients with HF.

Methods

We conducted a substudy of the prospective observational study comprising hospitalized patients with cardiovascular disease, who were admitted to the Cardiology Department of Tokyo Women's Medical University Hospital between June 2006 and April 2008. Patients with dementia, delirium, or other conditions (e.g. unconsciousness, intensive care, and end stage of another life-threatening disease) that make completing self-reported written questionnaires difficult were excluded. Among them, 221 patients with a New York Heart Association (NYHA) functional class ≥2 on admission, who were diagnosed with HF, and who completed the questionnaires were included in this study (Fig. 1). The details of the study have been reported elsewhere [26]. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients gave written informed consent.

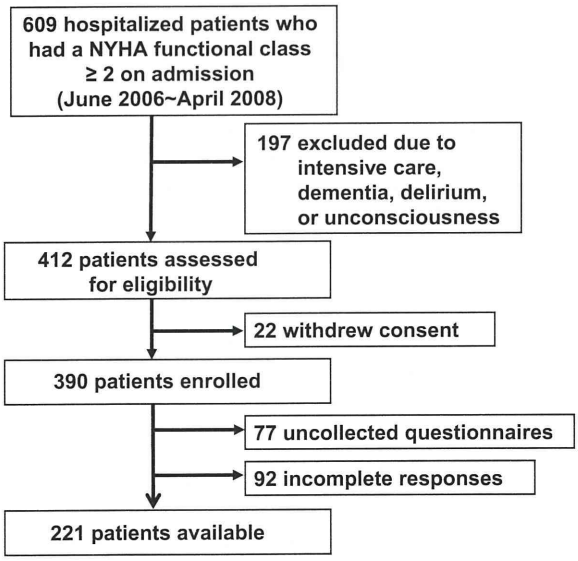


Fig. 1. The flow diagram of study subjects. NYHA, New York Heart Association.

Assessment of depression and anxiety

The majority of patients received the psychological questionnaires within 3 days (2 ± 1 days) after their admission to the hospital. For patients who initially required intensive treatment, these questionnaires were received after their transfer to the general cardiology ward. The Zung Self-Rating Depression Scale (SDS) was used to screen for depression and to measure the severity of the depression in a number of settings [27–31]. The Zung SDS is a self-reported scale containing 20 questions that assess the psychological and somatic symptoms. The Zung SDS score has been reported to be a primary discriminating variable in distinguishing depressed from non-depressed persons and indicates likelihood ratio positive for major depression as 3.3 [95% confidence interval (CI): 1.3–8.1] and likelihood ratio negative as 0.35 (95% CI: 0.2–0.8) [29]. The Zung SDS score has also been used to assess depression in clinical studies on cardiovascular diseases [32–36]. A cutoff index score of 60 has been shown to detect clinical depression while avoiding an abundance of false positives in sick patients [37–40]. In this study, depression was defined as a Zung SDS index score of ≥60.

The State-Trait Anxiety Inventory (STAI) was used to measure anxiety symptoms [41]. In this study, only the state-scale measurement was used because state anxiety is characterized as a temporary change in each patient's emotional state due to medical illness or other external cause, the measurement has also been used in clinical studies on cardiovascular diseases [16,20,42]. The STAI comprises 20 items, and each item is scored on a four-point scale from 1 (not at all) to 4 (very much so). The STAI scores range from 20 to 80, with higher scores indicating greater levels of anxiety. Anxiety was defined as a score of ≥40 (male) or ≥42 (female) [43,44].

Follow-up

After discharge, patients were seen as outpatients at our hospital or their general practitioner's clinic at 1- to 3-month intervals until October 2011. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT), and ICD, were also followed every 3–6 months at our pacemaker/ICD clinic. The information about deceased patients was obtained from the medical records, family members, their general practitioners, and the admitting hospital.

Clinical outcomes

The primary outcome was the composite of death from any cause and rehospitalization due to worsened HF and refractory arrhythmia from the time of enrollment to the first event. Worsened HF was defined by signs and symptoms, such as dyspnea, rales, and ankle edema, as well as by the need for treatment with diuretics, vasodilators, positive inotropic drugs, or an intra-aortic balloon pump. Refractory arrhythmia was defined as supraventricular or ventricular tachyarrhythmia that required external defibrillation or pacing, intravenous antiarrhythmics, such as amiodarone and nifekalant, catheter ablation, or implantation of an ICD, or bradyarrhythmia that required implantation of a pacemaker. Both supraventricular and ventricular arrhythmias are common in patients with HF, and cause symptoms, hemodynamic instability, and morbidities such as stroke and sudden death. Therefore, we included rehospitalization for refractory arrhythmia in

the primary endpoint. The second outcome was death from any cause.

Data analysis

The data are presented as either mean ± standard deviation (SD) or number of patients. We created four groups on the basis of depression and anxiety: (1) depression alone, (2) anxiety alone, (3) clustered depression and anxiety, and (4) no symptoms (no depression nor anxiety). Baseline clinical data were compared between the groups using analysis of variance (ANOVA). The Cox proportional hazards model was used to assess the relationship of depression, anxiety, and the cluster of both with clinical outcomes. We first assessed the unadjusted relationship of the following variables at discharge with the primary outcome: female gender, age ≥65 years, NYHA functional class, plasma B-type natriuretic peptide (BNP) concentration >250 pg/ml [45,46], implantation of an ICD/CRT with a defibrillator (CRT-D), left ventricular ejection fraction (LVEF) ≤35%, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula [47] <60 ml/min/1.73 m^2, depression, anxiety, and clustered depression and anxiety. Then, we assessed the relationship of depression, anxiety, and the cluster of both with the primary outcome after controlling for gender, age ≥65 years, NYHA functional class, BNP >250 pg/ml, implantation of an ICD/CRT-D, LVEF ≤35%, and eGFR <60 ml/min/1.73 m^2. The cumulative event-free rates were calculated using the Kaplan–Meier method. The data analyses were performed with SPSS (Statistical Package for the Social Sciences) statistical software (version 11.01, SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered significant.

Results

Patients

A total of 221 patients with HF who completed both the Zung SDS and STAI were included in this analysis. More than half of the patients (64%) had a non-ischemic etiology, and one-third had implanted cardiac devices. Five patients (2%) who were diagnosed with major depression by a psychiatrist had taken antidepressants (Table 1). In our sample, none of the patients with depression received non-pharmacological treatment such as cognitive behavior therapy.

Psychological distress and outcomes

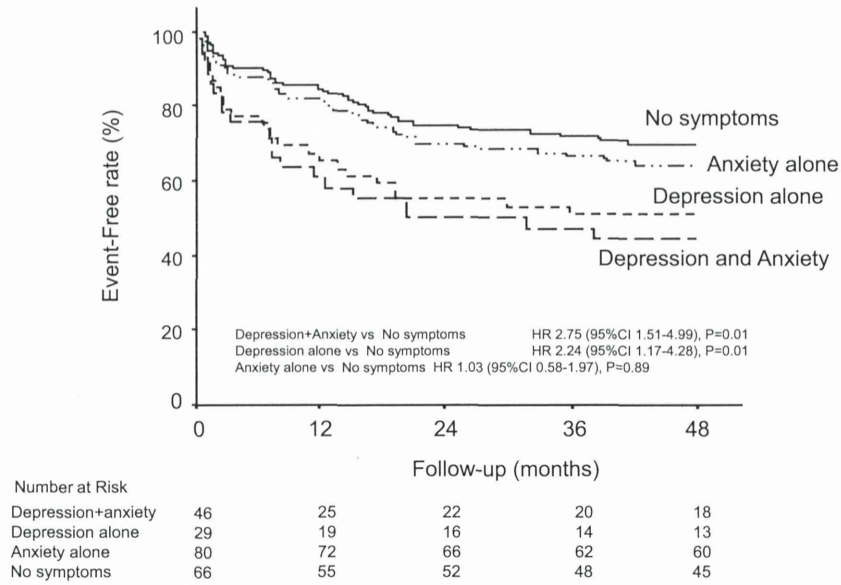
Overall, 75 patients (34%) were diagnosed as having depression and 126 patients (57%) as having anxiety. Among them, 29 patients (13%) had depression alone, 80 patients (36%) had anxiety alone, and 46 patients (21%) had both depression and anxiety (Table 1).

During an average follow-up of 41 ± 21 months, 69 patients (31%) met the primary outcome: 31 patients died and 38 patients required rehospitalization due to worsened HF or refractory arrhythmia. Kaplan–Meier curves for the primary outcome in the four groups are shown in Fig. 2. Patients with depression alone and those with clustered depression and anxiety were at an increased risk of the primary outcome [hazard ratio (HR) 2.24, 95% CI: 1.17–4.28, $p = 0.01$ and HR 2.75, 95% CI: 1.51–4.99, $p = 0.01$, respectively] compared to patients with no symptoms. Causes of death and rehospitalization are shown in Table 2. Kaplan–Meier curves for death from any cause are shown in Fig. 3. Patients with clustered depression and anxiety were at an increased risk of death

Table 1
Patient characteristics.

	Depression alone ($n = 29$)	Anxiety alone ($n = 80$)	Depression + anxiety ($n = 46$)	No symptoms ($n = 66$)	p value
Age (years)	61 ± 10	62 ± 14	60 ± 12	62 ± 12	0.18
Female	7 (24%)	22 (28%)	14 (30%)	19 (25%)	0.91
Underlying heart disease					0.01
Coronary artery disease	7 (24%)	20 (25%)	5 (11%)	39 (59%)	
Non-ischemic cardiomyopathy	11 (38%)	23 (29%)	37 (80%)	44 (67%)	
Valvular heart disease	10 (34%)	20 (25%)	2 (4%)	7 (11%)	
Congenital heart disease	0 (0%)	1 (1%)	2 (4%)	2 (3%)	
BNP on admission (pg/ml)	269 (84–709)	275 (4–2254)	349 (8–5271)	152 (4–8454)	0.01
BNP at discharge (pg/ml)	236 (48–826)	242 (18–1478)	288 (15–2326)	120 (5–4926)	0.01
NYHA functional class on admission (II/III/IV)	25/4/0	67/15/0	23/22/1	56/10/0	<0.01
NYHA functional class at discharge (II/III/IV)	27/2/0	77/3/0	30/15/1	64/2/0	<0.01
LVEF (%)	35 ± 10	38 ± 12	35 ± 15	39 ± 16	0.21
eGFR (ml/min/1.73 m^2)	72 ± 36	76 ± 38	70 ± 43	80 ± 38	0.16
Implanted cardiac devices					
Pacemaker/CRT-P	3 (10%)	5 (6%)	7 (15%)	7 (11%)	0.20
ICD/CRT-D	7 (24%)	18 (23%)	15 (33%)	15 (23%)	0.16
Comorbidities					
Hypertension	10 (34%)	31 (39%)	18 (39%)	25 (38%)	0.16
Diabetes	3 (10%)	27 (34%)	11 (24%)	28 (42%)	0.05
Major depression	1 (3%)	0 (0%)	3 (7%)	1 (2%)	0.04
Medications at discharge					
Beta-blockers	21 (72%)	59 (74%)	33 (72%)	43 (65%)	0.76
ACE inhibitors/ARBs	25 (86%)	69 (86%)	42 (91%)	59 (89%)	0.57
Spironolactone/eplerenone	16 (55%)	38 (48%)	30 (65%)	31 (47%)	0.15
Calcium channel blockers	16 (55%)	55 (69%)	19 (41%)	43 (65%)	<0.01
Aspirin	10 (34%)	29 (36%)	15 (33%)	33 (50%)	0.09
Warfarin	16 (55%)	42 (53%)	32 (70%)	22 (33%)	0.11
Amiodarone	11 (38%)	22 (28%)	20 (43%)	9 (14%)	<0.01
Antidepressants	1 (3%)	0 (0%)	3 (7%)	1 (2%)	0.16
Married	26 (90%)	73 (91%)	36 (78%)	64 (97%)	<0.01
Employed	13 (45%)	40 (50%)	13 (28%)	34 (52%)	0.04

Values are n (%) or mean ± SD or median (range).
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; CRT-D, CRT with a defibrillator; CRT-P, CRT with a pacemaker; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.



Number at Risk					
Depression+anxiety	46	25	22	20	18
Depression alone	29	19	16	14	13
Anxiety alone	80	72	66	62	60
No symptoms	66	55	52	48	45

Fig. 2. Kaplan–Meier curve for the primary outcome (death from any cause or rehospitalization due to worsened heart failure or refractory arrhythmia) in the four heart failure patient groups on the basis of depression and anxiety. HR, hazard ratio; CI, confidence interval.

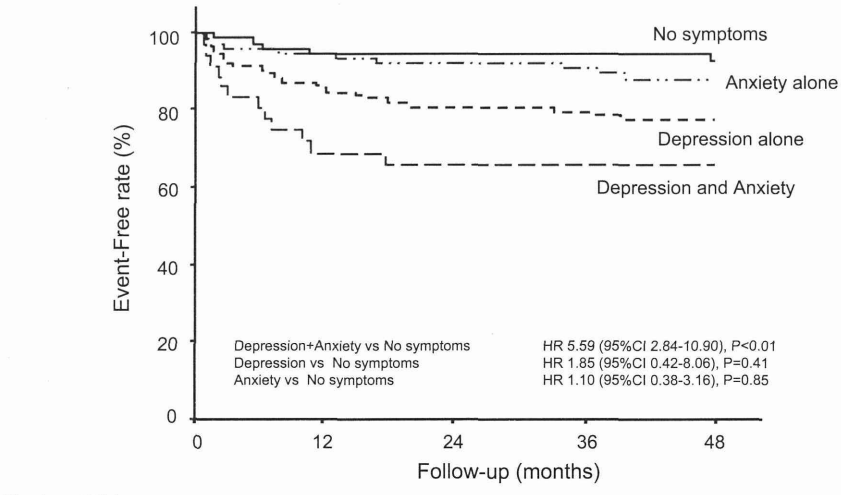
Table 2
Causes of death and rehospitalization for cardiac events.

	Depression alone ($n=29$)	Anxiety alone ($n=80$)	Depression + anxiety ($n=46$)	No symptoms ($n=66$)	p value
Death from any cause	8(28%)	4(5%)	17(37%)	2(3%)	<0.01
Cardiac death	8(28%)	4(5%)	16(35%)	2(3%)	<0.01
Sudden death	2(7%)	1(1%)	1(2%)	0(0%)	0.96
Heart failure	6(21%)	3(4%)	15(33%)	2(3%)	<0.01
Non-cardiac death	0(0%)	0(0%)	1(2%)	0(0%)	0.06
Hospitalization for heart failure	7(24%)	15(19%)	5(11%)	4(6%)	0.90
Hospitalization for refractory arrhythmia	3(10%)	2(3%)	1(2%)	1(2%)	0.29

Values are n (%).

from any cause (HR 5.59, 95% CI: 2.84–10.90, $p < 0.01$) compared to patients with no symptoms.

The univariate analysis showed that in addition to NYHA functional class, implantation of an ICD/CRT-D, LVEF ≤35%, BNP at discharge >250 pg/ml, eGFR <60 ml/min/1.73 m^2, depression alone, and a combination of depression and anxiety, but not anxiety alone, were significant predictors for the primary outcome (Table 3).



Number at Risk					
Depression+anxiety	46	31	29	29	29
Depression alone	29	24	22	21	20
Anxiety alone	80	71	64	60	60
No symptoms	66	56	55	55	53

Fig. 3. Kaplan–Meier curve for death from any cause in the four heart failure patient groups on the basis of depression and anxiety. HR, hazard ratio; CI, confidence interval.

Table 3
Univariate predictors for the primary outcome.

	Hazard ratio (95% CI)	*p* value
Female gender	0.70 (0.43–1.15)	0.16
Age ≥65 years	0.89 (0.56–1.42)	0.64
NYHA functional class at discharge	3.97 (2.61–6.04)	<0.01
Implantation of an ICD/CRT-D	4.26 (2.56–7.07)	<0.01
eGFR <60 ml/min/1.73 m^2	2.88 (1.81–4.59)	<0.01
BNP at discharge >250 pg/ml	2.95 (1.80–4.81)	<0.01
LVEF ≤35%	1.99 (1.24–3.19)	<0.01
Depression	2.59 (1.56–4.20)	<0.01
Anxiety	1.71 (0.98–2.98)	0.05
Depression and anxiety	2.63 (1.56–4.41)	<0.01

BNP, B-type natriuretic peptide; CRT-D, cardiac resynchronization therapy with a defibrillator; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Table 4
Relationship of depression and anxiety with the primary outcome after adjusting for age, gender, New York Heart Association class, device implantation, estimated glomerular filtration rate, B-type natriuretic peptide, and left ventricular ejection fraction.

	Hazard ratio (95% CI)	*p* value
Depression	1.69 (0.97–2.95)	0.06
Anxiety	1.46 (0.80–2.65)	0.21
Depression and anxiety	1.96 (1.00–3.27)	0.04

The relationship between depression and anxiety with the primary outcome after adjusting for age, gender, NYHA class, device implantation, eGFR, BNP, and LVEF revealed that patients with clustered depression and anxiety had an increased risk of the primary outcome, but depression alone was not related to the primary outcome (Table 4).

Discussion

Our study revealed that the prevalence of clustered depression and anxiety was 20% in hospitalized patients with HF. Furthermore, we found that patients with both depression and anxiety were at an increased risk of the primary composite outcome: death from any cause and rehospitalization due to worsened HF and refractory arrhythmia. Finally, clustered depression and anxiety, but not depression or anxiety alone, were shown to be independent factors associated with worsening clinical outcomes.

Several studies have shown that depression is an independent predictor of mortality in patients with HF [1–13]. In our study, depression was a risk factor in the univariate analysis but was not an independent factor after adjusting for clinical variables at discharge related to the primary outcome. There are a number of possible reasons for the differences in our results compared with those in the previous reports. First, our study had a high prevalence (one-third) of patients with an ICD/CRT-D. At present, an ICD is the principle therapy in HF patients for preventing sudden cardiac death. It is increasingly used due to the extended indication for primary prevention. However, ICD-specific problems, such as frequent shocks and a poor understanding of ICD therapy, increase depressive symptoms and reduce the quality of life for the ICD patients [39,48–50]. Our main study showed that an ICD implantation was significantly associated with depression [26]. Furthermore, the prevalence of depression increased as the NYHA functional class grade increased [4]. In our study, 18 of 23 patients (78%) with NYHA class III/IV at discharge were diagnosed with depression by the Zung SDS. The presence of an ICD/CRT-D and NYHA functional class III/IV may have confounded the association between depression and the primary outcome. Therefore, depression alone was thought not to be a predictor in this study after adjusting for multiple variables.

State anxiety is a transient mental or emotional reaction to several stressors, including medical illness. In a sense, it is thought to be a normal reaction in hospitalized patients and an inevitable result of hospitalization. A Japanese report showed that anxiety has been reported to be independently associated with rehospitalization due to worsened HF in outpatients with stable HF [44]. However, in general, an association between anxiety and mortality or long-term cardiac events in patients with HF has not been found [16–19]. Katon et al. suggested that the combination of depression and anxiety is associated with poor treatment adherence and increased medical complications in patients with chronic medical illness, which may be a severe consequence [51]. Anxiety and depression are different disorders, and the way in which their mechanisms may interact in the development of cardiac events or death are not understood. In the real world, however, psychological factors may cluster together within individuals to increase the risk of subsequent medical events [21]. There is a possibility that patients with higher psychological distress are selected by combining anxiety with depression.

In our study, HF was a major cause of death, and the rate of HF was significantly higher in patients with both depression and anxiety than in those with either depression or anxiety only or those with no symptoms. Although its pathophysiologic mechanisms are not completely understood, psychological distress may affect the treatment adherence behavior in patients with HF [52]. Poor adherence to treatment is associated with increased morbidity and mortality in patients with HF [53]. Clustered depression and anxiety can be a stronger predictive marker of the severity of the illness or poor prognosis than depression alone in hospitalized patients with HF. This cluster may also be an important marker for psychological distress, particularly in hospitalized patients with HF.

Study limitations

There were some limitations in this study. First, this was a single-center cohort study. The clinical characteristics of our patients might not reflect those of general cardiovascular patients with HF. Second, the patients admitted to our hospital were not consecutively enrolled in our main study. Many patients who received emergent or intensive care were not enrolled because they could not complete the questionnaires. Third, the questionnaires were not completed prior to discharge. The primary aim of our main study was to evaluate the prevalence and distribution of depression in hospitalized patients. Moreover, the length of the hospital stay in our patients ranged from a few days to several months because the severity of HF or comorbidities was heterogeneous. For a long-term prognosis, the assessment just before discharge might be more appropriate. However, previous studies have demonstrated that depression at the time of hospitalization, not prior to discharge, is associated with a poorer prognosis in patients with cardiovascular disease [54–57]. Fourth, the number of subjects was relatively small. Therefore, subgroup analysis was not feasible.

Conclusions

Our results showed that clustered depression and anxiety were predictors of death from any cause or rehospitalization due to worsened HF and refractory arrhythmia in patients with HF. This cluster may be an important marker for poor outcomes in patients with HF.

Conflict of interest

None declared.

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Brain Natriuretic Peptide in Acute Ischemic Stroke

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Elevated serum brain natriuretic peptide (BNP) levels are associated with cardioembolic stroke mainly because of atrial fibrillation (AF). However, the mechanisms of increased serum BNP levels are hitherto unclear. We aimed to identify the factors associated with increased BNP levels in patients with acute ischemic stroke. We measured serum BNP levels in consecutive patients aged 18 years or older. Stroke subtypes were classified using the Trial of ORG 10172 in Acute Stroke Treatment criteria. Categorical variables included age, sex, smoking status, alcohol consumption status, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease (CAD), AF, antiplatelet therapy, and anticoagulant therapy. Continuous variables included hemoglobin, creatinine (Cr), β-thromboglobulin, platelet factor 4, thrombin–antithrombin complex, and D-dimer levels. We further determined the relationship between serum BNP and intima–media thickness, left ventricular ejection fraction, size of infarction, National Institutes of Health Stroke Scale score on admission, and modified Rankin Scale (mRS) score at discharge. Of the 231 patients (mean age, 71 ± 12 years) with acute ischemic stroke (AIS), 36% were women. Serum BNP levels significantly correlated with CAD, AF, Cr, mRS, and cardioembolism (CE) (Dunnett method, $P = .004$). BNP levels were significantly higher in patients with larger infarcts, higher mRS scores, and higher $CHADS_2$ scores. The levels were higher in patients with larger infarcts, higher mRS scores at discharge, and higher $CHADS_2$ scores among AF patients. **Key Words:** Brain natriuretic peptide—acute ischemic stroke—atrial fibrillation—infarct size—$CHADS_2$ score—modified Rankin Scale.

Introduction

Brain natriuretic peptide (BNP), first isolated from porcine brains in 1988, is known to be of ventricular origin in humans and has been reported to be a useful marker of cardiac dysfunction.[1,2] Plasma BNP levels are also elevated in patients with acute ischemic stroke (AIS), particularly in those with atrial fibrillation (AF).[3-8] Recently, several studies have reported BNP levels to be predictive of AF after ischemic stroke or transient ischemic attack.[7-9] Elevated serum BNP levels, a powerful predictor of patient outcome in cardiovascular disease, have been associated with AF, cardioembolic stroke, and poststroke mortality. However, the mechanisms associated with

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increase in serum BNP levels are not well clarified. We aimed to identify the factors associated with increased BNP levels in patients with AIS.

Subjects and Methods

Subjects included 231 patients with AIS who had been consecutively admitted to our hospital between March 2010 and March 2012. Ischemic stroke was classified according to the Trial of ORG 10172 in Acute Stroke Treatment classification guidelines.[10]

The categorical variables used for statistical analysis included age, sex, current smoking status, alcohol consumption status, hypertension, diabetes mellitus (DM), dyslipidemia, coronary artery disease (CAD), and AF. Hypertension was defined as a blood pressure of 140/90 mm Hg or more at admission or despite receiving an antihypertensive agent. DM was defined as fasting blood glucose of 126 mg/dL or more or random blood glucose of 200 mg/dL or more and hemoglobin (Hb) A1c of 6.4% or more (The National Glycohemoglobin Standardization Program) at admission or despite receiving an antidiabetic agent. Dyslipidemia was characterized by serum low-density lipoprotein cholesterol of 140 mg/dL or more, high-density lipoprotein cholesterol of 40 mg/dL or less, or serum triglycerides of 150 mg/dL or more at admission or despite receiving antihyperlipidemic agents, such as statins or fibrates. CAD was defined as the detection of an ischemic alteration on electrocardiography or a history of any medical treatment for ischemic heart disease. AF was diagnosed by 24-hour ambulatory electrocardiographic monitoring, performed on admission. Antiplatelet therapy included treatment with aspirin, clopidogrel, cilostazol, or ozagrel (a thromboxane A2 synthase inhibitor), and anticoagulant therapy included treatment with heparin, warfarin, or argatroban (thrombin inhibitor).

The continuous variables used for statistical analysis included Hb, creatinine (Cr), β-thromboglobulin (β-TG), platelet factor 4 (PF4), thrombin–antithrombin complex (TAT), D-dimer, maximum intima–media thickness (IMT) of the bilateral carotid arteries by high-resolution duplex ultrasonography, and left ventricular ejection fraction by the modified biplane Simpson method[11] for transthoracic echocardiography. We evaluated the National Institutes of Health Stroke Scale (NIHSS) score for each patient on admission.[12] Outcomes were evaluated using the modified Rankin Scale (mRS) score at discharge or 2 months after stroke onset.[13] We also examined the correlation between BNP levels and $CHADS_2$ score in patients with AF.[14]

Magnetic Resonance Imaging

All magnetic resonance images were performed with 1.5 T scanners. Sequences included diffusion-weighted images (DWIs) obtained by spin-echo echo planar imaging (slice thickness, 7 mm; slice gap, 1.5 mm; field of view, 22 × 22 cm; acquisition matrix, 160 × 160/144 × 144/128 × 115; repetition time [TR], 3014-4500 ms; echo time [TE], 78-95 ms; b = .100 s/mm^2 in 3 diffusion-gradient directions), fluid attenuated inversion recovery images (slice thickness, 7 mm; slice gap, 1.5 mm; field of view, 22 × 22 cm; acquisition matrix, 224 × 272/209 × 256/205 × 256; TR, 6000-1000 ms; TE, 95-102 ms; inversion time, 2000-2600 ms), and T2-weighted images (slice thickness, 7 mm; slice gap, 1.5 mm; field of view, 22 × 22 cm; acquisition matrix, 320 × 416/224 × 256/205 × 256; TR, 3294-4000 ms, TE, 90-105 ms). Isotropic DWIs and apparent diffusion coefficient maps were automatically calculated.

Magnetic Resonance Image Assessment

Areas of hyperintensity on DWIs were used to diagnose AIS and classify infarct sizes. Signal increases solely attributable to T2 shine through were ruled out by comparison with apparent diffusion coefficient maps. We classified the infarcts into 3 groups: S (≤.3-1.5 cm), L (one third the size of the cerebral hemispheres), and M (sizes between S and L). S infarcts were .3-1.5 cm and M infarcts were more than 1.5 cm in the brain stem and cerebellar hemisphere.

Hemostatic Markers

Venous blood samples were collected at the time of admission for measuring hemostatic marker levels, including β-TG, PF4, TAT, and D-dimer. β-TG was measured using the Asserachrom β-TG kit (Diagnostica Stago, Asnieres, France); PF4, using an Asserachrom PF4 kit (Diagnostica Stago); TAT, using a Stacia Cleia TAT kit (Mitsubishi Chemical Medicine, Tokyo, Japan); and D-dimer, using the Nampia D-dimer kit (Sekisui Medical Co., Tokyo, Japan).

Measurement of Brain Natriuretic Peptide

Whole blood samples were collected at the time of admission. Plasma BNP levels were measured using a chemiluminescence enzyme immunoassay (Fujirebio, Inc., Tokyo, Japan). This assay uses 2 monoclonal antibodies against human BNP, one recognizing the carboxyl-terminal sequence and the other the ring structure of BNP, and measures BNP by sandwiching the molecule between the 2 antibodies.[15]

Evaluation of Carotid Atherosclerosis

Vascular risk factors were assessed, and ultrasound measurements of the common carotid artery (CCA) were performed using high-resolution, duplex ultrasonography (ALPHA 7; Hitachi Aloka ProSound, Tokyo, Japan) with a 13-MHz linear probe. We measured IMT in the bilateral CCAs, carotid bulbs, and internal carotid

arteries at carotid bifurcations. The IMT measurements were done following the Mannheim carotid IMT consensus.[16] Plaques were included when the maximum IMT was measured. We defined the maximum IMT as the largest IMT value in the bilateral CCAs, the carotid bulb, and the internal carotid arteries.

Echocardiography

An experienced sonographer performed the echocardiographic studies with a SONOS 5500 (Philips Medical Systems, Amsterdam, The Netherlands) or an ARTIDA (Toshiba Medical Systems, Tokyo, Japan) ultrasound system equipped with a 2- to 4-MHz phased-array transducer during continuous electrocardiographic recording.

Statistical Analysis

We examined the correlation of BNP levels with the categorical and continuous variables using regression analyses and performed multiple regression analysis for related factors (stepwise method). The statistical significance of the relationship between BNP levels and the ischemic stroke subtypes was determined using the Dunnett method. *P* values for trend tests were determined to assess the relationship between BNP levels and infarct sizes and mRS scores in all patients and between BNP levels and $CHADS_2$ scores in AF patients. All analyses were 2 sided, and the level of statistical significance was set at *P* less than .05. SAS software (version 9.1; SAS Institute, Cary, NC) was used for all analyses.

Results

The number of patients with small vessel occlusion (SVO), large artery atherosclerosis (LAA), cardioembolism (CE), and other abnormalities were 70, 86, 62, and 27, respectively. The background characteristics of patients in each ischemic stroke subtype are shown in Table 1.

Multiple linear regression analysis, with the stepwise method, demonstrated that Hb, CAD, AF, Cr, and mRS were independent significant variables for elevated BNP levels (Table 2). BNP was significantly higher in patients with CE than in those with SVO or LAA (Fig 1). BNP levels also increased as infarct size increased (Fig 2), and there was a significant positive correlation between BNP and mRS (Fig 3). Furthermore, BNP levels positively correlated with the $CHADS_2$ scores in AF patients (Fig 4).

Discussion

Independent factors significantly associated with a rise in BNP levels were CAD, AF, Cr, and mRS. Although left ventricular ejection fraction (LVEF) was not an independent factor associated with BNP levels in multivariate regression analysis, a significant correlation was observed between LVEF and BNP in the univariate regression

Table 1. *Patient characteristics*

	SVO	LAA	CE	Others	*P*
n	66	82	58	25	
Age	69.6 ± 12.6	72.1 ± 9.8	74.0 ± 10.9	62.1 ± 16.1	<.001
Men, %	66.7	67.1	58.6	60.0	.7
Current smoker, %	21.2	26.8	17.2	28.0	.533
Alcohol, %	22.7	12.2	15.5	20.0	.348
Hypertension, %	69.7	76.8	67.2	40	.007
Diabetes mellitus, %	28.8	52.4	36.2	16	.002
Dyslipidemia, %	40.9	59.8	34.5	32	.008
Coronary artery disease, %	15.2	22	8.6	4	.05
Atrial fibrillation, %	3	1.2	84.5	—	<.001
Antiplatelet therapy, %	27.3	37.8	22.4	20	.757
Anticoagulant therapy, %	3	2.4	31	—	.629
BNP (pg/mL)	29 (13-91)	54 (30-101)	202 (120-385)	12 (7-57)	<.001
β-TG (ng/mL)	118.7 ± 211.0	113.7 ± 114.4	94.0 ± 89.5	382.5 ± 117.6	.111
PF4 (ng/mL)	36.1 ± 65.3	36.3 ± 44.4	23.8 ± 26.1	124.0 ± 380.9	.1
TAT (ng/mL)	1.7 ± 1.7	4.1 ± 7.4	2.7 ± 3.0	4.2 ± 7.7	.175
D-dimer (μg/mL)	1.4 ± 2.4	6.8 ± 44.3	6.1 ± 26.2	2.8 ± 3.8	.713
MaxIMT (mm)	2.1 ± 2.0	3.4 ± 4.8	2.2 ± 1.2	1.4 ± 1.0	.03
LVEF	52.3 ± 6.9	50.2 ± 6.2	47.3 ± 8.1	52.9 ± 6.0	.056
NIHSS	2.0 ± 1.6	5.0 ± 4.5	6.5 ± 8.1	4.4 ± 5.1	<.001
mRS score (≤2), %	100	69.50	64.10	72.00	<.001

Abbreviations: BNP, brain natriuretic peptide; β-TG, β-thromboglobulin; CE, cardioembolism; PF4, platelet factor 4; TAT, thrombin–antithrombin complex; LAA, large artery atherosclerosis; LVEF, left ventricular ejection fraction; MaxIMT, maximum intima-media thickness; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SVO, small vessel occlusion.

Table 2. *Multiple linear regression analysis, with stepwise correlations, between BNP levels and categorical variables*

	Univariate regression coefficient	*P* value	Multivariate regression coefficient	*P* value
Age	3.4	.079		NS
Body weight	−2.67	.170		NS
Men	−64.59	.183		NS
Smoking status	−13.84	.806		NS
Alcohol consumption	5.16	.935		NS
Hypertension	24.93	.623		NS
Diabetes mellitus	−47.95	.315		NS
Dyslipidemia	−44.78	.110		NS
CAD	155.53	.001	209.79	.0076
AF	181.39	<.001	316.04	<.001
Antiplatelet therapy	−.13	.997		NS
Anticoagulant therapy	112.86	.122		NS
Hb	−42.02	<.001		NS
Cr	35.54	.001	89.72	.001
β-TG	.04	.857		NS
PF4	−13.84	.46		NS
TAT	4.33	.23		NS
D-dimer	−.07	.93		NS
MaxIMT	7.41	.331		NS
LVEF	−11.88	<.001		NS
NIHSS	7.45	.065		NS
mRS	50.77	.001	58.73	.014

Abbreviations: AF, atrial fibrillation; BNP, brain natriuretic peptide; β-TG, β-thromboglobulin; CAD, coronary artery disease; Cr, creatinine; Hb, hemoglobin; LVEF, left ventricular ejection fraction; mRS, modified Rankin Scale; MaxIMT, maximum intima–media thickness; NIHSS, National Institutes of Health Stroke Scale; NS, nonsignificant; PF4, platelet factor 4; TAT, thrombin–antithrombin complex.

analysis. CAD, however, was an independent factor for increased BNP levels. This might suggest the effects of other confounding factors except LVEF in patients with CAD.

Although they did not reach statistical significance, beta-TG and PF4 tended to be higher in patients with SVO and LAA. Increases in beta-TG and PF4 may reflect platelet activation associated with the formation of platelet-rich thrombi in arteries of patients with SVO and LAA.

The presence of AF is associated with higher circulating BNP levels,[17] and cardiac atria, which contain muscle mass much less than that in ventricles, may be the predominant source of BNP in AF patients. Natriuretic peptide levels progressively increase with renal dysfunction,[18] suggesting that chronic increased body fluid volume associated with renal dysfunction is related to

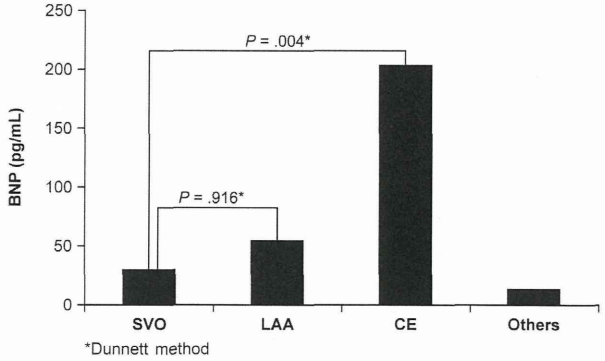

Figure 1. *Differences in BNP levels between subtypes of ischemic stroke. BNP levels were significantly higher in patients with CE than in those with SVO or LAA. Abbreviations: BNP, brain natriuretic peptide; CE, cardioembolism; LAA, large artery atherosclerosis; SVO, small vessel occlusion.*

increased left ventricular wall tension and, thereby, increased BNP levels. CAD, AF, and Cr are also associated with impaired cardiac function.

Makikallio et al[4] also found a relationship between increased mortality and high BNP levels in the acute phase of CE, and ventricular ejection fraction and expansion of left atrium diameter were associated with functional outcomes and mortality. There are other reports indicating that BNP levels are significantly higher in patients with CE than in those with other ischemic stroke subtypes.[3-8] Thus, BNP levels may be increased by cardiac dysfunction in patients with CE.

A correlation was demonstrated to exist between infarct size and BNP level in patients with AIS; infarct volumes, on DWIs, and admission NIHSS scores were also moderately correlated.[19] Plasma BNP levels are also markedly increased during the early phase of acute myocardial infarction.[20] Although the precise mechanisms by which BNP is synthesized and released remain to be elucidated, plasma BNP levels appear to reflect the degree of ventricular dysfunction during the subacute phase and to predict the prognosis of patients with myocardial infarction.[20]

BNP levels have recently been reported to be elevated in patients with subarachnoid hemorrhage,[21] suggesting

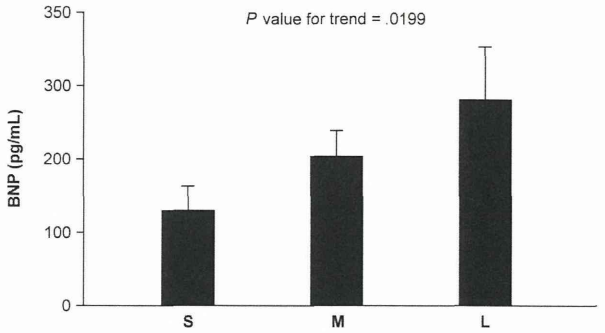

Figure 2. *Correlation between BNP levels and brain infarct sizes. S was of 1.5 cm or less, L involved more than one third of the cerebral hemispheres, and M was between S and L. BNP levels were higher in patients with larger infarcts. Abbreviation: BNP, brain natriuretic peptide.*